

CLAIMS

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1. A method of treatment of a chronic inflammatory disease⁽⁹⁵⁾ in a patient, the method comprising the administration to the patient of a compound that selectively inhibits cytokine-activated T cells (T_{ck} cells), by rendering the T_{ck} cells functionally inhibited with respect to their ability to activate monocytes and/or by reducing the number of the T_{ck} cells.
2. A method according to Claim 1 wherein said compound selectively inhibits T_{ck} cell-induced release of one or more pro-inflammatory cytokines from monocytes.
3. A method according to Claim 2 wherein the cytokine is tumour necrosis factor- α .
4. A method according to any one of Claims 1 to 3 wherein said compound is an antibody-like molecule having specificity for T_{ck} cells.
5. A method according to Claim 4 wherein the antibody-like molecule is selected from the group of molecules consisting of Fab molecules, $F(ab')_2$ molecules, Fv molecules, disulphide-linked Fv molecules, single chain Fv (scFv) molecules and single domain antibodies (dAbs).
6. A method according to any one of Claims 1 to 5 wherein said compound is a nucleic acid molecule encoding a polypeptide which selectively inhibits T_{ck} cells.

7. A method of identifying a compound with efficacy in the treatment of a chronic inflammatory disease comprising the step of testing the compound for an ability to selectively inhibit cytokine-activated T cells (T_{ck} cells) *in vitro*.
8. A method according to Claim 7 wherein testing the compound for an ability to selectively inhibit T_{ck} cells comprises testing the compound for an ability to selectively inhibit T_{ck} cell-induced release of one or more pro-inflammatory cytokines from monocytes.
9. A method according to Claim 8 wherein the cytokine is tumour necrosis factor- α .
10. A method according to any one of Claims 7 to 9 wherein said method comprises the following steps:
- (i) pre-incubating T_{ck} cells with a compound to be tested either prior to fixation or during their activation in culture;
- (ii) resuspending said T_{ck} cells in the absence of the test compound;
- (iii) stimulating monocytes by co-culturing with said resuspended T_{ck} cells; and
- (iv) assaying for TNF α production by said stimulated monocytes.
11. A method according to any one of Claims 7 to 10 wherein the chronic inflammatory disease is a disease of humans.

12. A method according to any one of Claims 7 to 11 wherein the chronic inflammatory disease is rheumatoid arthritis.
13. A method according to any one of Claims 7 to 12 wherein testing the compound for an ability to selectively inhibit T_{ck} cells or selectively inhibit T_{ck} cell-induced release of one or more pro-inflammatory cytokines from monocytes comprises determining whether the compound exhibits NF-κB inhibition.
14. A method according to Claim 13 wherein NF-κB inhibition is constituted by a reduction in the binding of nuclear extracts, derived from monocytes exposed to the compound, to an NF-κB promoter DNA oligonucleotide.
15. A method according to Claim 14 wherein a reduction in the binding of nuclear extracts, derived from monocytes exposed to the compound, to an NF-κB promoter DNA oligonucleotide is determined by an electrophoretic mobility shift assay (EMSA).
16. A method according to any one of Claims 13 to 15 wherein NF-κB inhibition is deemed to exist if the binding of NF-κB to an NF-κB promoter DNA oligonucleotide is reduced to no more than 50%, preferably no more than 20%, 10%, 5% or 1%, and most preferably is substantially zero.
17. A method according to Claim 13 wherein NF-κB inhibition is constituted by a reduction in expression of the NF-κB gene.

18. A method according to Claim 17 wherein a reduction in the expression of the NF- κ B gene is determined by a reporter gene assay.

19. A method according to Claim 18 wherein the reporter gene assay comprises coupling a β -galactosidase gene to the NF- κ B gene and determining a reduction in β -galactosidase activity.

20. A method according to Claim 19 wherein β -galactosidase activity is reduced to no more than 50%, preferably no more than 20%, 10%, 5% or 1%, and most preferably is substantially zero.

21. A method according to any one of Claims 7 to 12 wherein testing the compound for an ability to selectively target T_{ck} cells or selectively inhibit T_{ck} cell-induced release of one or more pro-inflammatory cytokines from monocytes comprises determining whether the compound exhibits PI3 kinase activation.

22. A method according to Claim 21 wherein PI3 kinase activation is constituted by an increase in PI3 kinase activity in monocytes exposed by the compound.

23. A method according to Claim 22 wherein PI3 kinase activation is deemed to exist if there is an increase in PI3 kinase activity equivalent to at least 50% of the increase induced by IL-10 stimulation (100 ng/ml for 2 minutes), preferably at least 70%, 80% or 90%, and most preferably greater than the increase induced by IL-10 stimulation.

24. A compound identified as having efficacy in the treatment of a chronic inflammatory disease by a method according to any one of Claims 7 to 23.
25. An antibody-like molecule having specificity for cytokine-activated T cells (T_{ck} cells).
26. An antibody-like molecule according to Claim 25 selected from the group of molecules consisting of Fab molecules, $F(ab')_2$ molecules, Fv molecules, disulphide-linked Fv molecules, single chain Fv (scFv) molecules and single domain antibodies (dAbs).
27. An antibody-like molecule according to Claim 25 or 26 wherein said antibody-like molecule is humanised.
28. A method of making an antibody-like molecule according to any one of Claims 25 to 27 comprising immunising an animal with a population of cytokine-activated T cells (T_{ck} cells).
29. An isolated cell that expresses an antibody-like molecule according to any one of Claims 25 to 27.
30. An isolated cell according to Claim 29 wherein the cell is a hybridoma cell.
31. A method for identifying an antibody-like molecule according to any one of Claims 25 to 27 comprising the following steps:
- (i) providing a population of cytokine-activated T cells (T_{ck} cells); and

(ii) using said T_{ck} cells to screen a library of antibody-like molecules.

32. A method according to Claim 31 wherein the antibody-like molecule library is a phage display library.

33. A compound comprising a target cell specific portion and a directly or indirectly cytotoxic portion, wherein the target cell specific portion comprises an antibody-like molecule according to any one of Claims 25 to 27.

34. A compound according to Claim 33 wherein the cytotoxic portion is a directly cytotoxic portion selected from the group consisting of radionuclides, ricin, ribonuclease, deoxyribonuclease, and *Pseudomonas* exotoxin A.

35. A compound according to Claim 34 wherein the cytotoxic portion is indirectly cytotoxic.

36. A compound according to Claim 35 wherein the cytotoxic portion is capable of inducing apoptosis of the target cells.

37. A compound according to any one of Claims 33 to 36 wherein the cytotoxic portion is an enzyme.

38. A compound according to any one of Claims 33 to 37 wherein the target cell specific portion and the cytotoxic portion are fused.

39. A compound according to Claim 38 wherein the target cell specific portion and the cytotoxic portion are separated by a linker sequence.
40. A nucleic acid molecule encoding a compound according to Claim 38 or 37.
41. A vector comprising a nucleic acid molecule according to Claim 40.
42. A host cell line comprising a vector according to Claim 41.
43. A pharmaceutical formulation comprising an antibody-like molecule according to any one of Claims 25 to 27 or a compound according to any one of Claims 24 or 33 to 39 and a pharmaceutically acceptable carrier.
44. An antibody-like molecule according to any one of Claims 25 to 27 or a compound according to any one of Claims 33 to 39 for use in medicine.
45. A compound according to Claim 24 for use in the treatment of a chronic inflammatory disease.
46. Use of an antibody-like molecule according to any one of Claims 25 to 27 or a compound according to any one of Claims 24 or 33 to 39 in the preparation of a medicament for the treatment of a chronic inflammatory disease.
47. A method of treating a patient with a chronic inflammatory disease comprising administering to said patient a therapeutically effective amount of an antibody-like molecule according to any one of Claims 25 to 27 or a compound according to any one of Claims 33 to 39.

48. The use according to Claim 46 wherein the chronic inflammatory disease is rheumatoid arthritis.

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